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NEW SOVIET DATA ON ANTIBIOTICS

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This is a general review of recent progress in the field of antibiotics. In compiling this review, particular attention has been paid to questions of general theoretical interest, as well as to results which indicate new ways of testing and investigating antibiotics in clinical practice.

A. Antibiotics of a Polypeptidic Nature

Many new antibiotics of a polypeptidic nature have been isolated recently both from animal and plant sources. An investigation of the chemical structure of these antibiotics showed that the individual amino acids are not disposed in the form of a straight chain, but cyclically, so that the molecule forms a closed ring. The theory of the cyclic structure of proteins, which was advanced by Zelinskiy and Gavrilov /4/, found complete confirmation in results of the investigation of antibiotics.

Antibiotics of a polypeptidic nature are formed principally by various sporiferous aerobic bacteria which are found in the soil An example is bacitracin, which is chemically a polypeptide composed of at least nine amino acids: isoleucine, aspartic acid, phenyl alanine, leucine, glutamic acid, lysine, histidine, cystine, and ornithine.

USSR gramicidin (gramacidin S) has a still simpler constitution. It is a crystalline polypeptide consisting of five amino acids (valine, ornithine, leucine, phenyl alanine, and proline) which form a ring. The chemical composition of gramicidin S was investigated by Belozerskiy and Paskhina (cf Znamenskaya, Agatov, and Belozerskiy). /10/

The cyclic structure of gramicidin S is of decisive importance for its antibacterial action. A synthetic straight chain pentapeptide was prepared from the same amino acids which enter into the composition of gramicidin S.

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The optical configuration was also the same. Nevertheless, the synthetic pentapeptide has only a very weak effect on bacteria. Although one gamma of gramicidin S per milliliter suppresses the growth of staphylococci, 2,000 gammas of the synthetic polypeptide per milliliter are necessary for that purpose. In other words, the synthetic straight chain substance is 2,000 times less effective than the natural antibiotic.

The cyclic polypeptide gramicidin S contains four amino acid molecules of the natural l-configuration, and one molecule of an amino acid (phenyl alanine) of the d-configuration which usually does not occur in nature.

The antibiotic enniantin [31] is also a cyclic polypeptide. It forms a 12-membered ring in which l-amino acids are partly replaced by d-hydroxy acids.

B. Families of Similar Antibiotics

Strains of Bacillus polymyxa yield a whole group of substances which have antibiotic properties and are called polymyxins. [23] All polymyxins are closely similar and all of them are polypeptides, but the amino acid composition of polymyxins formed by different strains is different. All polymyxins contain threonine and diaminobutyric acid, but three other amino acids (leucine, serine, and phenyl alanine) are not obligatory components of the molecule of the antibiotic. They are specific constituents of individual variations of polymyxins of different origin. Depending on the composition, the pharmacological properties of the polymyxins vary.

Penicillin K (heptyl-penicillin) is considerably less effective clinically than penicillin G (benzyl-penicillin). While penicillin K is rapidly decomposed by a thermolabile enzyme contained in blood serum and tissues of various organs, penicillin G is stable and is not affected by this enzyme. [6,20]

The effect of streptomycin B (mannosidostreptomycin) is three times weaker than that of streptomycin A.

C. New Data Obtained in Study of Penicillin

The immunological state of the organism has an effect on the therapeutic action of penicillin, as could be shown by penicillin therapy of pneumococcal infection in normal rats and in rats weakened by a protein-deficient diet. [33] While penicillin was effective in curing the infection of normal rats, it was less effective in the case of rats that had been exposed to protein starvation. The starved rats had a lowered capacity for the formation of antibodies and a reduced phagocytary activity.

The fact that there is an optimum concentration of penicillin and of other antibiotics above which the antibacterial effect diminishes [25] is significant. There is no clear explanation for this phenomenon at present.

As far as the mechanism of the action of penicillin on the metabolism of the bacterial cell is concerned an extensive amount of valuable experimental data is now being accumulated. [3, 7, 8, 9, 13, 15, 19, 21] Thus, it was established that in staphylococci which perish from the effect of penicillin, the metabolism of nucleic acids is gravely disturbed. This is reflected in the fact that the percentage of extractable nucleotides rises sharply in staphylococci which had been exposed to the action of penicillin. This rise apparently occurs because the rate of polymerization has dropped, not because the rate of synthesis has been accelerated. It remains to be proved that the process is a primary one rather than the result of some other primary disturbance of metabolism caused by penicillin.

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From this viewpoint the study of the metabolism of microorganisms which have acquired resistance to penicillin is of particular interest. It has been established that staphylococci which are sensitive to penicillin must assimilate amino acids from the surrounding nutritive medium. The same staphylococci, after becoming resistant to penicillin, no longer require amino acids assimilated from the surrounding medium: they have acquired the ability to synthesize them inside the cell from sugar and inorganic salts. These observations show that penicillin specifically suppresses some phase of the assimilation of amino acids required by the bacterial cell.

Lately, new experimental data have been obtained which confirm this conclusion. Thus, the ordinary gram-negative pathogenic bacterium Salmonella typhimurium is a typical heterotrophic form which does not have to assimilate amino acids from the outside for its nutrition. At the same time, this bacterium is extremely resistant to penicillin. However, under laboratory conditions one may develop strains of this microorganism which have lost the ability to synthesize the amino acid cysteine and are unable to grow in a nutritive medium that does not contain cysteine. Such strains of Salmonella typhimurium, which must assimilate cysteine from the solution in which they are cultivated, become very sensitive to the action of penicillin.

Notwithstanding the interesting and convincing character of these data, many peculiarities of the action of penicillin still remain unexplained. For instance, why does penicillin suppress so strongly the growth of the hay bacillus, which is a typical hetrotrophic bacterium able to synthesize within the cell from glucose and inorganic salts, all organic substances needed by it?

Currently, an increasing amount of data is being collected which indicates that changes in the metabolism of bacteria alter their sensitivity to penicillin. /28/

D. New Data Obtained in the Study of Streptomycin

New methods of purifying streptomycin from inert ballast substances by transferring it into organic solvents with the aid of detergents /29/ deserve attention. There is no doubt that similar transfer agents can be applied in the purification of other antibiotics.

A number of recent investigations has been devoted to the study of streptomycin from the microbiological point of view. /16, 17, 18/ It is a characteristic trait of this antibiotic that bacteria get accustomed to it very quickly and develop forms which are resistant to it. Particularly striking results are observed when chromogenic bacteria are modified under the action of streptomycin into streptomycin-resistant varieties which sharply differ in appearance and metabolism from the original form sensitive to streptomycin. Thus, the streptomycin-resistant variety of the blue pus bacillus loses the capacity to form blue pigment. Furthermore, the rate of growth of this microorganism drops sharply also the activity of its dehydrogenase. The streptomycin-resistant variety of Euglena gracilis loses its ability to form chlorophyll. This shows that adaptation to an antibiotic is connected with alterations in the metabolism of the microorganism.

In some cases, streptomycin-dependent varieties of bacteria are developed under the action of antibiotics as well as streptomycin-resistant forms. The streptomycin-dependent strains cannot exist in nutritive media which lack streptomycin. Thus, by cultivating B. coli in a medium containing streptomycin, one may develop a strain which requires this antibiotic for its growth.

The streptomycin-dependent strains can be utilized for the identification of streptomycin. If streptomycin is added to a culture bouillon and the bouillon is seeded with a streptomycin-dependent strain of B. coli, the bacillus will propagate. If the substance which had been added differs from streptomycin,

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the bacillus will not propagate. By this method, one can easily dete streptomycin in the culture media of various fungi isolated from the soil, so that the detection of new active fungi-producing streptomycin is facilitated.

On the whole the easy adaptation of bacteria to streptomycin brings more disappointments to the clinician than advantages to the microbiologist. Many species of rapidly growing pathogenic bacteria acquire resistance to streptomycin so fast that threatment with this substance becomes useless. It is fortunate that the slowly growing tuberculosis bacilli become adapted to streptomycin at a much lower rate of speed.

The rate at which bacteria become adapted to streptomycin is of vital importance for the selection of a rational course of treatment with this antibiotic. In tuberculosis the results of streptomycin therapy are usually apparent after 6-7 weeks of treatment. If at the expiration of this time most of the bacteria have been suppressed by the antibiotic and only a small number that are resistant to streptomycin survives, the surviving microorganisms, generally speaking, cannot interfere with the over-all clinical improvement of the patient's condition.

Development of streptomycin-resistant forms of tuberculosis bacilli is fully compatible with clinical improvement and recovery of the patient as a result of treatment with the antibiotic, because the total number of bacteria is sharply reduced by the action of streptomycin, while the resistant bacilli are suppressed by the protective forces of the organism. /14/ However, if the resistant forms of bacilli should be transferred to another person and should produce disease in that person, the new case of infection would not be susceptible to treatment with streptomycin because of the absence of bacilli that are sensitive to the antibiotic. This condition implies that further successes of streptomycin therapy may be seriously endangered. Under the circumstances, one should use streptomycin only when therapy with this antibiotic is actually indicated: otherwise we will merely expedite the spreading of streptomycin-resistant forms of tuberculosis bacilli.

Another drawback of streptomycin is its side effect on the vestibulary apparatus. However, a method for reducing the toxicity of streptomycin (by hydrogenation) has been developed. Dihydrostreptomycin can be administered in much larger doses than streptomycin without any ill effects. /26/

The effectiveness of streptomycin can be increased by administering it together with potassium iodide. Clinicians know that after administration of iodine tubeculosis bacilli appear in the sputum, where they were formerly absent. It is assumed that iodine contributes to the caseous decay of tubercles, and that as a result of this process bacilli are released. Upon release they are more readily attacked by any effective therapeutic agent.

While solutions of potassium iodide do not reinforce the action of streptomycin on tuberculosis bacilli in vitro, experiments on infected guinea pigs yielded encouraging results. Potassium iodide was administered to the guinea pigs per os in aqueous solution. Every guinea pig received 80 mg per kilogram of weight per day. While potassium iodide alone did not suppress the development of the tuberculosis infection to any extent, as compared with control animals, the therapeutic effect of streptomycin was considerably enhanced when potassium iodide was administered. In a series of experiments the lethality in the control group was 100%, in the group treated with streptomycin alone 46% and among animals which underwent combined treatment with streptomycin and potassium iodide 14%.

At present, it is necessary to check these results in clinical practice. If the effective daily dosis of streptomycin, which comprises one gram for the treatment of tuberculosis, can be lowered considerably by adding potassium iodide, the undesirable side effects of this antibiotic will be reduced, so that the therapy of tuberculosis with this drug will consequently become much more effective.

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A new important field for the application of streptomycin is the treatment of gastroenterites of the newborn. These infections are caused by B. paracoli, Proteus, and other gram-negative bacteria. They result in a high percentage of lethality. Administration of streptomycin per os in such cases gives positive results and rapidly frees the intestine of gram-negative microorganisms. When applied in this manner, streptomycin has a purely local action, because it is not resorbed at all from the gastrointestinal tract. However, it suppresses the intestinal gram-negative flora and in a number of cases brings about clinical improvement of the patient's condition. A drawback of streptomycin in this application is the rapid adaptation of coli bacilli to it. If the bacteria have not been suppressed during the first 24 hr after the start of the treatment, it is difficult after this point to exert any action on the streptomycin-resistant flora.

E. New Antibiotics From Cultures of Actinomycetes

Among new antibiotics isolated from actinomycetes one may note neomycin [30] and borrelidin.[22]

F. New Antibiotics Which Suppress Rickettsia (Chloromycetin and Aureomycin)

Recently, two new antibiotics, chloromycetin [3] and aureomycin [24, 27] were isolated, described, and tested clinically. Both of them are now being applied therapeutically. These two substances contain nonionic chlorine.

Chloromycetin is being produced synthetically. In the synthesis of this antibiotic, the racemic form is obtained. The racemic form could be separated into the two enantiomorphs, of which the one having the d-configuration corresponds to natural chloromycetin produced by the fungus Actinomyces venezuelae. The antibiotic action of the synthetic d-isomer is exactly equal to that of natural chloromycetin, while the l-isomer is devoid of any antibiotic activity. Furthermore, the configuration of the d-isomer is opposed to that of most naturally occurring substances (cf. l-ephedrine or l-alanine). This shows that optical inversion [with respect to naturally occurring substances] is not limited to penicillin, streptomycin, and gramicidin, but occurs quite generally in antibiotics and has a direct relation to the mechanism of the antibiotic effect. As a result of optical inversion, antibiotics are foreign to levorotatory protein, and thus may selectively suppress some enzymatic processes in microorganisms.[5]

G. New Applications of Soviet Gramicidin [Gramicidin S]

The mechanism of the action of gramicidin S on various bacteria has been thoroughly investigated in recent work.[2, 10, 11] Clinical work done by USSR investigators has opened new fields for the application of this antibiotic. Of the greatest interest is utilization of gramicidin for the treatment of bacillary and amoebic dysentery. It has been originally used for this purpose by A. I. Baldina and I. A. Kozlov at Professor Tareyev's clinic.[1]

Experience acquired in treating bacillary dysentery with sulfa drugs shows that the process of anatomic recovery, i.e., of the healing of dysenteric ulcers in the intestine, lags to a considerable extent behind the disappearance of the basic symptoms of the disease which corresponds to clinical recovery. With sulfa drug therapy, clinical recovery takes place, on the average, on the third or fourth day from the beginning of treatment, while the healing of ulcers on the mucous membrane of the intestine occurs much later, on the average, at the expiration of 3 weeks from the beginning of treatment. Transition of the disease into a protracted and chronic state is apparently connected with the presence of slowly healing ulcers on the mucous membrane of the intestine.

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While sulfa drugs effectively heal the clinical symptoms of dysentery, they have only a slight effect on the healing of ulcers. Under the circumstances, the search for therapeutic agents which would expedite the healing of ulcers is of great importance if the transition of dysentery from an acute disease into a chronic disease is to be prevented.

Gramicidin S has a strong bactericidal effect on dysentery bacilli and gram-positive bacteria. In the treatment of dysentery, aqueous solutions of gramicidin have been applied in the form of enemas in combination with sulfa drug therapy.

It has been established by Baladina and Kozlov that in patients treated with gramicidin all basic pathological symptoms of dysentery disappear twice as fast as in patients treated with sulfa drugs only. Treatment with gramicidin shortens the period of clinical recovery and accelerates the healing of ulcers in the intestine. This healing becomes noticeable even in the first days after the beginning of the treatment.

In recent years, USSR medical men and scientists have contributed a considerable amount of new and original results in connection with the use of gramicidin S in clinical practice. In some suppurative processes, the use of gramicidin yields even better results than the application of penicillin. This experience has been summarized in L. N. Kuzmenko's interesting monograph on the subject.[12]

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